Factors Associated with Improvement and Worsening of Visual Acuity 2 Years after Focal/Grid Photocoagulation for Diabetic Macular Edema

Published in final edited form as:
Ophthalmology. 2010 May ; 117(5): 946–953. doi:10.1016/j.ophtha.2009.10.002.

Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema

Lloyd Paul Aiello, MD[1], **Allison R. Edwards, MS**[2], **Roy W. Beck, MD, PhD.**[2], **Neil M Bressler, MD**[3], **Matthew D. Davis, MD**[4], **Frederick Ferris**[5], **Adam R. Glassman, M.S**[2], **Michael S. Ip, MD**[4], and **Kellee M. Miller, M.P.H.**[2] **for the Diabetic Retinopathy Clinical Research Network**

[1]Joslin Diabetes Center and Department of Ophthalmology, Harvard Medical School

[2]Jaeb Center for Health Research

[3]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore

[4]University of Wisconsin School of Medicine and Public Health

[5]National Eye Institute/National Institute of Health

Abstract

Purpose—To identify factors associated with the visual acuity outcome following focal/grid photocoagulation for diabetic macular edema (DME) among eyes randomized to the focal/grid photocoagulation treatment group within the Diabetic Retinopathy Clinical Research Network (DRCR.net) trial comparing triamcinolone with focal/grid laser.

Design—Multicenter, randomized clinical trial.

Participants—Three hundred thirty eyes with DME assigned to the focal/grid photocoagulation group, visual acuity 20/40 to 20/320 and optical coherence tomography (OCT) central subfield thickness ≥250 microns.

Methods—Eyes were treated with a protocol-defined photocoagulation technique, which was repeated at 4-month intervals for persistent or recurrent edema. Separate logistic regression models were used to evaluate the associations of demographic, clinical, OCT, and fundus photographic variables with visual acuity improvement or worsening of 10 or more letters from baseline to 2 years. The association of the initial visual acuity outcome after treatment with the subsequent visual acuity course also was evaluated.

Main Outcome Measures—Visual acuity measured with the electronic Early Treatment Diabetic Retinopathy Study method.

Corresponding author: Allison R. Edwards, M.S., c/o Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647; Phone: (813) 975-8690, Fax: (800) 816-7601, drcrstat1@jaeb.org.

A published list of the Diabetic Retinopathy Clinical Research Network investigators and staff participating in this protocol can be found in *Ophthalmology 2008;115:1447-9, 1449 e1-10* with a current list available at www.drcr.net (Accessed August 26, 2009).

An address for reprints is not provided.

Results—Worse baseline visual acuity was the only factor found to be associated with more frequent visual acuity improvement (P<0.001), and both greater baseline OCT-measured retinal volume (P=0.001) and better baseline visual acuity (P=0.009) were found to be associated with more frequent visual acuity worsening. Visual acuity outcomes were similar in eyes with and without prior macular or panretinal photocoagulation. The initial visual acuity outcome at 4 months was not generally predictive of the subsequent course. Many eyes that worsened 10 or more letters from baseline to 4 months subsequently improved, and many eyes that initially improved, subsequently worsened.

Conclusions—At this time, focal/grid photocoagulation remains the standard management for DME and these results do not alter this paradigm.

Introduction

Despite recent attempts at strict glycemic control and optimization of other important systemic parameters such as hypertension and hyperlipidemia, diabetic retinopathy continues to be a leading cause of new onset vision loss worldwide in the working age population.[1-3] Although severe vision loss can occur from proliferative diabetic retinopathy, diabetic macular edema (DME) accounts for the majority of vision loss.[4, 5] The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated the efficacy of focal/grid photocoagulation in reducing the risk of moderate vision loss from DME.[6] However, in the two decades since the completion of ETDRS, diabetic patient care approaches have evolved substantially.[1] The beneficial outcomes of focal/grid laser in an era of improved glycemic control were confirmed and expanded in recent clinical trials conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net).[7, 8] At this time, no ocular treatment for DME has been demonstrated to have a better long-term outcome than focal/grid photocoagulation.

In an effort to identify factors associated with the visual acuity outcome following focal/grid photocoagulation for DME, we performed additional analyses on the 330 eyes that were randomized to the laser group of a multicenter, randomized clinical trial comparing focal/grid photocoagulation with intravitreal triamcinolone.

Methods

Of the 840 eyes (of 693 subjects) enrolled in the DRCR.net "Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema", 330 eyes (one eye of 330 subjects) were randomly assigned to focal/grid photocoagulation. These eyes form the cohort evaluated in the current report. The primary trial outcome was assessed at two years. The detailed methods of this study have been published previously, [8, 9] with the full protocol available at www.drcr.net (Accessed August 26, 2009).

Briefly, the trial was designed to determine whether visual acuity at 2 years was better in eyes with center-involved DME treated with intravitreal preservative-free triamcinolone (1 mg or 4 mg) as compared with focal/grid laser. Individuals were eligible if they were 18 years of age or older with type 1 or 2 diabetes. Study eye eligibility criteria included best corrected electronic ETDRS visual acuity letter score between 73 and 24 (approximate Snellen equivalents 20/40-20/320), macular edema on exam involving the fovea, optical coherence tomography (OCT) central subfield thickness ≥ 250 microns, and no prior or anticipated need for scatter photocoagulation for proliferative diabetic retinopathy (PDR) within 4 months of the baseline study visit. Patients were ineligible if they had undergone any prior treatment with intravitreal corticosteroids or pars plana vitrectomy, recent treatment with peribulbar corticosteroids or laser photocoagulation, or a history of glaucoma or treatment for steroid-induced intraocular pressure elevation.

Focal/grid photocoagulation was performed at baseline by the treatment technique described in Table 1. This technique is modified from the published ETDRS protocol to be representative of the technique in most common use today as determined by a survey of DRCR.net investigators and is referred to as focal/grid photocoagulation.[10-14] Retreatment was performed at 4-month intervals for persistent or recurrent DME unless one or more of the following deferral criteria were met: (1) OCT central subfield of 225 μm or less, visual acuity score >= 79 (approximate Snellen equivalent of ~20/25), or substantial improvement in macular edema (>= 50% decrease in OCT central subfield thickening) with expectation of further improvement without additional laser; (2) contraindication to further laser based on an adverse event from previous laser or the investigator's judgment that maximum safe laser already had been performed; or (3) apparent futility of additional laser as defined by at least an 8-month period over which laser was given twice with less than a 5 letter improvement in the visual acuity score and lack of decrease in OCT central subfield thickness of at least 50 microns, representing at least a 20% reduction in retinal thickening. An eye assigned to the laser group could receive alternative treatment (e.g., intravitreal triamcinolone) if it experienced at least a 15 letter decrease from baseline in best corrected visual acuity that was sustained over 2 consecutive 4 month intervals and if the decrease was due to OCT-documented persistent or recurrent macular edema. Forty three (13%) of the 330 eyes received treatment for DME other than laser (study intravitreal triamcinolone, nonstudy triamcinolone [Kenalog], vitrectomy, or bevacizumab) within the two-year period.

Statistical Methods

Separate logistic regression models were used to evaluate the association of baseline clinical, OCT, and fundus photographic variables (see tables 2-5 for listing of variables evaluated) with visual acuity improvement (10 or more letters) or worsening (10 or more letters) from baseline to 2 years. Factors with a p value <0.10 were evaluated in multivariate models, with a final model consisting of factors with a p value <0.01 following a backwards selection process. The last-observation-carried forward method was used for imputation when the 2-year visual acuity score was missing. Similar results were produced when analyses were limited to subjects who completed the two year exam.

All reported *P* values are two-sided and unadjusted for multiple comparisons. In view of the large number of variables evaluated, only associations with p values <0.01 were considered unlikely to be due to chance. Statistical analyses were conducted utilizing SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Mean age of the 330 subjects was 63 years; 50% were women and 74% Caucasian. Type 1 diabetes was present in 4% and type 2 diabetes in 96%. Prior macular photocoagulation had been performed in 198 (60%) of the eyes.

Two-year follow up was completed by 272 (82%) of the 330 subjects. Among the 58 subjects with incomplete follow up, 20 (34%) died prior to two years and the others either withdrew from the study or were lost to follow up. On average, the subjects who completed two years of follow up had 2.9±1.4 [standard deviation (SD)] focal/grid photocoagulation treatments over the course of 2 years. The number of focal/grid photocoagulation treatments performed during the study in the 169 subjects who had undergone macular photocoagulation prior to enrolling in this study did not differ substantially from the number received by the 103 subjects who were laser naïve at study entry (mean 2.8±1.3 versus 3.1±1.6, P=0.15 by t test).

Baseline Factors and Visual Acuity Outcome

Visual acuity improved from baseline to 2 years by 10 or more letters in 32% of eyes and worsened by 10 or more letters in 19% of eyes. Numerous factors were evaluated for their association with improvement or worsening of visual acuity. These included demographics and medication use (Table 2), ocular characteristics and prior laser therapy (Table 3), OCT findings (Table 4) and photographic ocular characteristics (Table 5). In a multivariate model (Table 6), the only factor found to be statistically significantly ($p < 0.01$) associated with visual acuity improvement (10 or more letter gain from baseline) was baseline visual acuity (worse baseline visual acuity was associated with greater improvement, $P<0.001$). Of note, visual acuity improvement was not associated with baseline OCT-measured retinal thickness or with whether macular photocoagulation or panretinal photocoagulation previously had been received. A loss of 10 or more letters was associated in the multivariate model with baseline OCT-measured retinal volume (greater retinal volume was associated with more frequent visual acuity worsening, $P=0.001$) and baseline visual acuity (better visual acuity was associated with more frequent visual acuity worsening, $P=0.009$).

Visual Acuity Outcome According to Initial Response

The proportion of eyes with a 10 or more letter improvement gradually increased over the two years of follow up while the proportion with a 10 or more letter loss was fairly similar from 4 months to 2 years (Figure 1). At 4 months, 47 eyes (18%) had an improvement in the visual acuity letter score ≥10 from baseline, 172 (65%) had a letter score within 9 of baseline, and 45 (17%) had a letter score ≥10 worse than baseline. As shown in Table 7, eyes that had worsened from baseline to 4 months were more likely to improve than worsen further from 4 months to 2 years, whereas eyes that had improved or changed less than 10 letters and had visual acuity worse than 20/32 at 4 months were about equally likely to improve or worsen by 10 letters between four months and two years. Eyes that had visual acuity 20/32 or better at 4 months were more likely to worsen than improve between 4 months and 2 years, as expected due to the ceiling on achieving additional substantial improvement.

Discussion

Since focal/grid photocoagulation is the current standard care for DME, we conducted an analysis in an attempt to identify factors associated with improvement and with worsening of visual acuity after laser treatment. The results of these analyses were more remarkable for the factors that were not associated with the visual acuity outcome following focal/grid photocoagulation rather than the factors that were associated. We evaluated factors potentially correlated with improvement and worsening separately, believing that different factors might be associated with each direction of change. Not surprisingly, the likelihood of improving 10 or more letters (2 or more lines) was greater when baseline visual acuity was poor and the likelihood of worsening 10 or more letters was greater when baseline visual acuity was good. This likely reflects, at least in part, ceiling and floor effects on the amount of improvement that can occur when acuity is only mildly reduced and the amount of worsening that can occur when visual acuity is poor. Thicker retinas at baseline were more likely to lose vision than thinner retinas after adjusting for visual acuity, perhaps reflective of a group of eyes with more severe and/or longer standing disease.

Because of the large number of variables evaluated, we only considered associations with a p value <0.01 to be significant. Nevertheless, there were few variables that even met a 0.05 p value threshold. No demographic factors, factors related to diabetes (type, duration, HbA1c, systolic or mean arterial blood pressure), OCT morphologic assessments (cystoids abnormalities, subretinal fluid, vitreoretinal abnormalities) or fundus photograph assessments (retinopathy severity, hemorrhage, microaneurysms, exudates, surface wrinkling) were

statistically associated with the visual acuity outcome. The sample size was large and the tightness of the confidence intervals on the point estimates of association (odds ratios) indicate that it is unlikely that meaningful associations were undetected. Of note, the probability of improvement was similar in eyes that had and had not received prior macular photocoagulation; eyes that had been treated with laser 3 or more times in the past had a similar chance of visual acuity improvement as eyes that had not had prior laser treatment. This finding suggests that there is value in continuing to administer additional focal/grid photocoagulation as long as edema is still present and it is possible to place additional burns. We also assessed whether change in visual acuity at 4 months was predictive of change at two years but we could not identify a clear pattern. Many eyes that worsened 10 or more letters from baseline to 4 months subsequently improved and many eyes that initially improved, subsequently worsened.

The strengths of this study were the large number of DME eyes with standardized baseline measurements, treated with a standardized focal-grid photocoagulation protocol and prospectively followed with standardized measurements of visual acuity. This represents the largest cohort of such eyes since the ETDRS was conducted. The two-year completion rate of 88% (excluding deaths) is less than optimal. However, analyses with and without imputation for missing data provided similar results and there is not a clear reason to expect that the missing data biased the results. The potential role of retinal nonperfusion could not be assessed since flourescein angiography was not required as part of this study.

At this time, focal/grid photocoagulation is the only ocular treatment that has been demonstrated to be effective for DME. Our results and the results from the ETDRS have not demonstrated any subgroups of patients for whom treatment is contraindicated.

Acknowledgments

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, U.S. Department of Health and Human Services EY14231, EY14269, EY14229.

The funding organization participated in oversight of the conduct of the study and review of the manuscript but not directly in the design of the study, the conduct of the study, data collection, data management, data analysis, interpretation of the data, or preparation of the manuscript.

Allergan, Inc. provided the triamcinolone and topical antibiotics after successfully competing for a request for proposals issued by DRCR.net for a company to provide a preservative-free triamcinolone for the study. As per the DRCR.net Industry Collaboration Guidelines (available at www.drcr.net), the DRCR.net had complete control over the design of the protocol, ownership of the data, and all editorial content of presentations and publications related to the protocol. Allergan, Inc. has provided unrestricted funds to DRCR.net for its discretionary use.

A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net (Accessed August 26, 2009).

References

1. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. Arch Ophthalmol 1995;113:36–51. [PubMed: 7826293]
2. Klein, R.; Klein, BE. Vision disorders in diabetes. In: National Diabetes Data Group. , editor. Diabetes in America. 2nd. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 1995 [August 21, 2009]. p. 293-338.NIH publ. no. 95–1468 Available at: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter14.pdf
3. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XXII. The twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008;115:1859–68. [PubMed: 19068374]

4. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464–74. [PubMed: 6521986]

5. Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology 1998;105:998–1003. [PubMed: 9627648]

6. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology 1991;98:766–85. [PubMed: 2062512]

7. Diabetic Retinopathy Clinical Research Network (DRCR.net). Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol 2009;127:245–51. [PubMed: 19273785]

8. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–9. [PubMed: 18662829]

9. Ip MS, Bressler SB, Antoszyk AN, et al. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features. Retina 2008;28:919–30. [PubMed: 18698292]

10. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–806. [PubMed: 2866759]

11. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 2. Ophthalmology 1987;94:761–74. [PubMed: 3658348]

12. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report no. 4. Int Ophthalmol Clin 1987;27:265–72. [PubMed: 3692708]

13. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991;98:741–56. [PubMed: 2062510]

14. Writing Committee for the Diabetic Retinopathy Clinical Research Network. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Arch Ophthalmol 2007;125:469–80. [PubMed: 17420366]

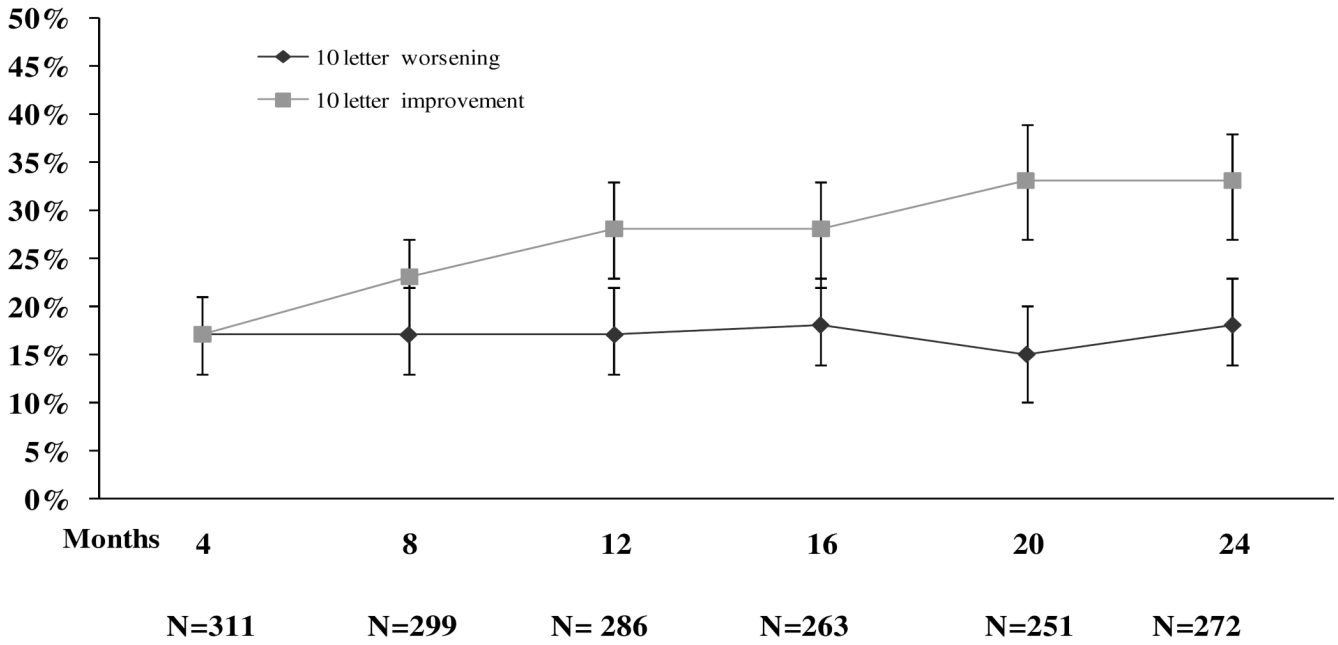

Figure 1.
Change in visual acuity (10 letter improvement and 10 letter worsening) from baseline to each visit through 2 years. The bars represent 95% confidence intervals.

Table 1

Comparison of the Modified-Early Treatment Diabetic Retinopathy Study (ETDRS) and ETDRS Focal/Grid Photocoagulation Techniques

Burn Characteristic	Focal / Grid Photocoagulation (modified-ETDRS technique)	ETDRS Technique
Area Considered for Treatment	500 to 3000 microns from the center of macula. No burns are placed within 500 microns of optic disk.	Initially same. However, if vision is < 20/40 and retinal edema/leakage persists, lesions >300 microns from the macular center are treated unless there is perifoveal capillary dropout.
Wavelength:	Green or yellow	Blue-green or green
Burn Size	50 microns	Focal: 50-100 microns Grid: <200 microns
Burn Duration	0.05 to 0.1 sec	Same
Grid Treatment	If fluorescein angiography is performed: apply to all areas of diffuse leakage or nonperfusion within the area noted above as well as to all areas with retinal thickening within the area noted above If fluorescein angiography is not performed: apply to all areas with retinal thickening within the area noted above	Same
Burn Intensity	Barely visible (light grey)	"Mild" intensity (More intense than modified-ETDRS technique)
Burn Separation	2 visible burn widths apart	At least 1 burn width apart
Focally Treat Leaking Microaneurysms	All leaking microaneurysms are focally treated, but only in areas of retinal thickening located within treatment area noted above	Same. In addition, optional treatment of focal lesions > 3,000 microns from the center if prominent leaks present and associated with thickening or hard exudates extending closer to the center
Change Microaneurysms Color	Not required, but at least a mild burn should be evident beneath all Microaneurysms	Recommended whitening or darkening of large Microaneurysms (Microaneurysms > 40 microns)

ETDRS =Early Treatment Diabetic Retinopathy Study

Table 2

Change in Visual Acuity from Baseline to 2 Years According to Baseline Demographics and Medications

	N	10 Letter Gain	Odds Ratio (95% Confidence Interval)	P-Value*	10 Letter Loss	Odds Rati (95% Confidence Interval)	P-Value*
Gender				0.94			0.74
Women	166	31%	0.98 (0.62, 1.56)		18%	0.91 (0.52, 1.58)	
Men	164	32%	1.00		20%	1.00	
Race/Ethnicity				0.20			0.29
Black/African American	31	32%	1.05 (0.47, 2.33)		6%	0.27 (0.06, 1.15)	
Hispanic or Latino	39	23%	0.66 (0.30, 1.46)		21%	1.00 (0.43, 2.30)	
Other	17	53%	2.47 (0.92, 6.65)		12%	0.52 (0.11, 2.33)	
White	243	31%	1.00		21%	1.00	
Diabetes Type				0.81			0.80
Type 1	14	29%	0.86 (0.27, 2.82)		21%	1.19 (0.32, 4.39)	
Type 2	316	32%	1.00		19%	1.00	
Diabetes Duration†				0.41			0.75
<15 years	154	32%	1.09 (0.68, 1.73)		17%	0.79 (0.45, 1.38)	
≥15 years	176	31%	1.00		20%	1.00	
HbA1c†				0.14			0.30
<7.5	133	34%	1.00 (0.60, 1.66)		17%	0.90 (0.48, 1.70)	
≥7.5	133	34%	1.00		18%	1.00	
Blood Pressure - systolic							
≥ 140	166	30%	0.88 (0.55, 1.40)	0.91	19%	0.99 (0.57, 1.71)	0.79
<140	164	33%	1.00		19%	1.0	
Blood Pressure – mean arterial							
≥100	149	33%	1.12 (0.70, 1.79)	0.65	17%	0.85 (0.49, 1.49)	0.89
<100	181	30%	1.00		20%	1.00	
Prescribed Glitazones				0.82			0.93
No	225	31%	0.94 (0.57, 1.55)		19%	0.98 (0.54, 1.76)	
Yes	105	32%	1.00		19%	1.00	
Prescribed Statins				0.24			0.81
No	142	35%	1.35 (0.85, 2.15)		18%	0.95 (0.54, 1.66)	

	N	10 Letter Gain	Odds Ratio (95% Confidence Interval)	P-Value*	10 Letter Loss	Odds Rati (95% Confidence Interval)	P-Value*
Yes	188	29%	1.00		19%	1.00	

*Unadjusted P-values from logistic regression models (missing and cannot grade values are excluded from models)

†Continuous version of variable used in model to obtain P-value. Categories are shown for presentation purpose only§Mean Arterial Pressure=Diastolic + 1/3(Systolic-diastolic)

Missing or nongradable data for HbA1c (64).

Last observation carried forward method used to impute missing 2-year visual acuity scores for 58 eyes.

Table 3

Change in Visual Acuity from Baseline to 2 Years According to Baseline Ocular Characteristics and Prior Laser Therapy

	N	10 Letter Gain	Odds Ratio (95% Confidence Interval)	P-Value*	10 Letter Loss	Odds Ratio (95% Confidence Interval)	P-Value*
Visual Acuity†				<0.0001			0.07
60-73 letters (20/32-2 to 20/63)	189	23%	0.39 (0.24, 0.62)		23%	2.07 (1.14, 3.77)	
24-59 letters (20/63-1 to 20/320-1)	141	43%	1.00		13%	1.00	
Lens Status				0.45			0.54
Phakic	262	31%	0.81 (0.46, 1.41)		19%	1.25 (0.61, 2.56)	
Pseudophakic	68	35%	1.00		16%	1.00	
Diabetic Retinopathy Severity‡				0.18			0.20
Microaneurysms only, mild or moderate nonproliferative diabetic retinopathy	67	31%	1.46 (0.72, 2.97)		12%	0.53 (0.21, 1.30)	
Moderately severe or severe nonproliferative diabetic retinopathy	163	36%	1.76 (0.98, 3.17)		21%	1.03 (0.54, 1.95)	
Mild, moderate, or high-risk proliferative diabetic retinopathy	88	24%	1.00		20%	1.00	
Number of Prior Sessions of Macular Laser‡				0.71			0.25
0	132	32%	1.28 (0.64, 2.56)		23%	1.35 (0.61, 3.00)	
1	95	32%	1.26 (0.61, 2.63)		17%	0.93 (0.39, 2.22)	
2	47	36%	1.55 (0.67, 3.58)		13%	0.67 (0.23, 2.02)	
3 or more	56	27%	1.00		18%	1.00	
Prior Panretinal Photocoagulation				0.07			0.13
No	277	34%	1.93 (0.95, 3.92)		20%	1.99 (0.81, 4.88)	
Yes	53	21%	1.00		11%	1.00	

*Unadjusted P-values from logistic regression models (missing and cannot grade values are excluded from models)

†Continuous version of variable used in model to obtain P-value. Categories are shown for presentation purpose only

‡Ordinal version of variable used in model to obtain P-value

Missing or nongradable data for diabetic retinopathy severity (12).

Last observation carried forward method used to impute missing 2-year visual acuity scores for 58 eyes.

Table 4

Change in Visual Acuity from Baseline to 2 Years According to Baseline Optical Coherence Tomography Findings

	N	10 Letter Gain	Odds Ratio (95% Confidence Interval)	P-Value*	10 Letter Loss	Odds Ratio (95% Confidence Interval)	P-Value*
OCT Central Subfield Thickness†				0.63			0.23
<400 microns	166	31%	1.19 (0.67, 2.13)		16%	0.67 (0.34, 1.31)	
400-500 microns	80	36%	1.48 (0.77, 2.88)		23%	1.05 (0.50, 2.20)	
>500 microns	83	28%	1.00		22%	1.00	
OCT Retinal Volume†				0.45			0.01
<9.2 mm^3	140	31%	0.97 (0.59, 1.59)		16%	0.68 (0.38, 1.24)	
≥9.2 mm^3	143	32%	1.00		22%	1.00	
OCT Cystoid Abnormalities‡				0.72			0.88
No evidence	12	17%	0.35 (0.07, 1.87)		17%	1.12 (0.19, 6.72)	
Questionable	26	27%	0.65 (0.21, 1.98)		19%	1.33 (0.34, 5.21)	
Definite, centrally located, no extension beyond central 1mm	182	35%	0.95 (0.44, 2.05)		18%	1.24 (0.45, 3.45)	
Definite, centrally located, no extension beyond central 2mm	74	24%	0.56 (0.23, 1.36)		23%	1.67 (0.56, 4.99)	
Definite, centrally located, extend beyond central 2 mm	33	36%	1.00		15%	1.00	
OCT Subretinal Fluid‡				0.51			0.63
No evidence	235	31%	0.82 (0.47, 1.42)		18%	0.88 (0.46, 1.70)	
Questionable	20	30%	0.79 (0.27, 2.30)		20%	0.98 (0.29, 3.38)	
Definite	74	35%	1.00		20%	1.00	
OCT Vitreoretinal Abnormalities‡				0.56			0.37
No evidence	215	33%	1.08 (0.56, 2.08)		20%	1.82 (0.73, 4.55)	
Questionable	60	25%	0.73 (0.32, 1.68)		23%	2.28 (0.81, 6.46)	
Definite	51	31%	1.00		12%	1.00	

*Unadjusted P-values from logistic regression models (missing and cannot grade values are excluded from models)

†Continuous version of variable used in model to obtain P-value. Categories are shown for presentation purpose only

‡Ordinal version of variable used in model to obtain P-value

OCT= Optical Coherence Tomography

Missing or nongradable data for OCT CSF thickness (1), OCT retinal volume (47), OCT cystoid abnormalities (3), OCT subretinal fluid (1), OCT vitreoretinal abnormalities (4).

Last observation carried forward method used to impute missing 2-year visual acuity scores for 58 eyes.

Table 5

Change in Visual Acuity from Baseline to 2 Years According to Baseline Photographic Ocular Characteristics

	N	10 Letter Gain	Odds Ratio (95% Confidence Interval)	P-Value*	10 Letter Loss	Odds Ratio (95% Confidence Interval)	P-Value*
Hemorrhages/Microaneurysms in Grid (Photographic)‡				0.74			0.06
None§	2	100%	--		0%	--	
Definite, < mildest standard for hemorrhages/microaneurysms	23	22%	0.54 (0.17, 1.68)		22%	0.76 (0.24, 2.41)	
Definite, < intermediate standard for hemorrhages/ microaneurysms	244	32%	0.90 (0.49, 1.66)		17%	0.55 (0.28, 1.09)	
Definite, >= intermediate standard for hemorrhages/ microaneurysms	56	34%	1.00		27%	1.00	
Hard Exudates in Grid (Photographic)3				0.08			0.42
None	48	21%	0.52 (0.25, 1.08)		23%	1.37 (0.65, 2.88)	
Questionable/ definite	275	34%	1.00		18%	1.00	
Hard Exudates in Center (Photographic)3				0.04			0.12
None	139	24%	0.54 (0.33, 0.88)		19%	1.02 (0.58, 1.79)	
Questionable/definite	184	38%	1.00		18%	1.00	
Surface Wrinkling Retinopathy (Photographic)‡				0.12			0.54
None	273	34%	1.85 (0.91, 3.77)		19%	1.27 (0.56, 2.85)	
Questionable/ cellophane reflex/ subtle membrane/obvious membrane	51	22%	1.00		16%	1.00	

*Unadjusted P-values from logistic regression models (missing and cannot grade values are excluded from models)

‡Ordinal version of variable used in model to obtain P-value

§Two photos where hemorrhages/microaneurysms in grid were graded as “None” were excluded from the univariate model for that factor.

Missing or nongradable data for photo hemorrhages/MA in grid (5), photo hard exudates in grid (7), photo hard exudates in center (7), photo surface wrinkling retinopathy (6).

Last observation carried forward method used to impute missing 2-year visual acuity scores for 58 eyes.

Table 6
Multivariate Model for 10 Letter Gain and 10 Letter Loss at 2 Years

	Univariate Model *P* value	Multivariate Model* *P* value	Final Multivariate Model† *P* Value
A. 10 or More Letter Improvement from Baseline to 2 Years			
Prior Panretinal Photocoagulation	0.07	0.05	
Visual Acuity‡	<0.001	<0.001	<0.001
Hard Exudates in Grid (Photographic) §	0.08	0.34	
Hard Exudates in Center (Photographic) §	0.04	0.25	
B. 10 or More Letter Worsening from Baseline to 2 Years			
Visual Acuity‡	0.07	0.008	0.009
OCT Retinal Volume‡	0.01	0.006	0.001
Hemorrhages/Microaneurysms in Grid (Photographic) §	0.06	0.23	

*includes all factors that were P<0.10 in the univariate models; for factors with missing data, an indicator for missing data was added to the model

†includes factors that remained in the multivariate model after a backward selection process using P<0.01 to stay in the model

‡continuous version of variable used

§ordinal version of variable used

OCT= Optical Coherence Tomography

Table 7

Visual Acuity Change from Baseline to 4 Months Versus Change from 4 Months to 2 Years*

	Change in Visual Acuity Letter Score from Baseline to 4 Months				
	≥10 improved	±9	≥10 improved	±9	≥10 worse
	≥20/32 at 4 months	≥20/32 at 4 months	<20/32 at 4 months	<20/32 at 4 months	<20/32 at 4 months
	N=18	N=33	N=29	N=139	N=45
Change in Visual Acuity (letters) From 4 Months to 2 Years					
Mean (Standard Deviation)	-4 (10)	-2 (9)	0 (10)	1 (14)	8 (25)
Median (25^{th}, 75^{th} percentile)	-3 (-11, 2)	-1 (-9, 5)	1 (-8, 7)	2 (-4, 9)	10 (-1, 20)
***Distribution of Change** - (%)*					
≥ 15 letter improvement	0	0	7%	10%	31%
14-10 letter improvement	6%	6%	3%	14%	20%
9-5 letter improvement	17%	21%	28%	17%	13%
Same ± 4 letters	44%	42%	31%	35%	18%
5-9 letters worse	6%	6%	14%	7%	0%
10-14 letters worse	17%	15%	7%	9%	4%
≥ 15 letters worse	11%	9%	10%	7%	13%
***Distribution of Change** - (%)*					
≥ 10 letter improvement	6%	6%	10%	24%	51%
Same ± 9 letters	67%	70%	72%	59%	31%
≥ 10 letters worse	28%	24%	17%	17%	18%

*includes only those subjects with a visit at both 4 months and 2 years